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Cost-Effectiveness of Treatment for Pediatric Immune Thrombocytopenia

Rapid Review

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Abbreviations

EPAG	eltrombopag
ITC	indirect treatment comparison
ITP	immune thrombocytopenia
PSA	probabilistic sensitivity analyses
ROMI	romiplostim
TPO-R	thrombopoietin receptor
W&R	watch-and-rescue
WTP	willingness-to-pay

Key Messages

- Limited evidence from 1 cost-consequence analysis study showed that eltrombopag was the preferred thrombopoietin receptor agonist over romiplostim (i.e., less expensive and more effective) for treatment of chronic immune thrombocytopenia in pediatric patients.
- No cost-effectiveness studies of dapsone or rituximab were identified.

Context and Policy Issues

Immune thrombocytopenia (ITP) affects approximately 5 in 100,000 children per year, with a peak incidence occurring in children between 2 and 5 years of age.[1,2] ITP is an autoimmune disorder characterized by accelerated destruction of platelets, a risk of increased bleeding caused by platelet deficiencies (i.e., platelet count drops below 10 to 20 × 10^9 platelets/L).[3] Of the cases, 75% to 80% can be self-resolved within 6 months,[3] with some resolving within a year after diagnosis.[4] Approximately 20% to 30% of pediatric ITP patients could not have spontaneous remission and the disease became chronic.[3] Most patients present with mild bruising, and about 3% had serious bleeding from the nose, mucosa, and gastrointestinal tract.[5] Intracranial hemorrhage is the most serious complication of ITP, with the rates ranging from 0.17% to 0.6% among cases.[1,6,7] The cause of ITP remains unclear, although it can be triggered by viral infection, environmental factors, or immune defect.[8]

There are various ITP therapies available for preventing bleeding episodes by increasing platelet counts. Three commonly used first-line treatments for ITP are glucocorticoids, IV immunoglobulin, and anti-D immunoglobulin.[8] Glucocorticoids (e.g., prednisone or dexamethasone) have both rapid and delayed effects in increasing platelet counts, but most patients relapse after the steroids are discontinued.[9] Prolonged use of glucocorticoids has been associated with adverse side effects of steroids.[9] IV immunoglobulin has been shown to be superior to glucocorticoids or no treatment in early recovery of platelet counts within 24 hours of administration.[9] The exact mechanism of action of immunoglobulin is not well understood, although evidence has suggested that immunoglobulin slows down the destruction of platelets by inhibiting macrophage-induced phagocytosis.[9] Anti-D immunoglobulin is an antibody against the Rhesus (Rh)-positive blood type. It works by binding to Rh-positive red blood cells, the complex of which then binds to the Fc receptors on macrophages, which induces the destruction of red blood cells, thus sparing the removal of antibody-coated platelets.[9] Anti-D antibody is ineffective in patients with Rh-negative blood types and is contraindicated in patients with anemia.[9]

In patients having inadequate response to first-line therapies and still being treated with ITP for more than 3 to 6 months, second-line drugs may be considered.[10] They are rituximab, thrombopoietin receptor (TPO-R) agonists, and splenectomy.[10] Splenectomy is highly effective for inducing remission ITP and does not require maintenance therapy.[10] Although highly effective, splenectomy is associated with increased risk of infections, especially bacterial sepsis.[10] It is recommended to delay splenectomy in children for at least 12 months after initial ITP diagnosis, because some patients can achieve remission regardless of the choice of therapy.[11] Rituximab is a monoclonal antibody to CD20, which targets and destroys autoantibody-producing B lymphocytes.[9] The initial response rate of rituximab in children with chromic ITP is 40% to 50%, and the response rate at 2 to 5 years follow-up was only 25%.[12,13] TPO-R agonists such as eltrombopag (EPAG) and romiplostim (ROMI), which

stimulate megakaryocytes to increase the production of platelets, are emerging effective drugs for treatment of chronic ITP.[14] EPAG (brand name Revolade) has been approved by Health Canada for the treatment of ITP in adult and pediatric patients who have had an insufficient response to corticosteroids or immunoglobulins.[15] ROMI (brand name Nplate) has also been approved by Health Canada for the treatment of ITP in adult patients, but not in children, with chronic ITP.[16] The advantage of EPAG over ROMI is that EPAG is administered orally, while ROMI is administered weekly via injection.[10] Evidence has shown that both EPAG and ROMI appear to be effective treatment options for children with chronic ITP, but the their long-term efficacy and safety remain unclear.[17] Other drugs including mycophenolate mofetil, mercaptopurine, cyclosporin, and dapsone has been used to treat pediatric ITP, but the rate of efficacy of these drugs was generally low.[10]

Numerous studies have assessed the cost-effectiveness of various therapies in the treatment of ITP.[18-25] However, these studies did not consider pediatric patients.

The aim of this report is to summarize the evidence regarding the cost-effectiveness of dapsone, rituximab, and TPO-R agonists for pediatric patients with ITP.

Research Questions

1. What is the cost-effectiveness of dapsone for pediatric patients with ITP?
2. What is the cost-effectiveness of rituximab for pediatric patients with ITP?
3. What is the cost-effectiveness of TPO-R agonists for pediatric patients with ITP?

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including MEDLINE, Embase, the Cochrane Database of Systematic Reviews, the International HTA Database, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were thrombocytopenia and specific treatments (dapsone, rituximab, and thrombopoietin receptor agonists). CADTH-developed search filters were applied to limit retrieval to economic studies. Comments, newspaper articles, editorials, letters, and conference abstracts were excluded. Where possible, retrieval was limited to the human population. The search was completed on March 28, 2022 and limited to English-language documents published since January 1, 2012.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for

inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, or they were published before 2012.

Critical Appraisal of Individual Studies

The included publication was critically appraised by 1 reviewer using the Drummond checklist[26] for economic evaluations. Summary scores were not calculated for the included study; rather, the strengths and limitations were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 157 citations were identified in the literature search. Following screening of titles and abstracts, 148 citations were excluded and 9 potentially relevant reports from the electronic search were retrieved for full-text review. No potentially relevant publications were retrieved from the grey literature search for full-text review. Of these potentially relevant articles, 8 publications were excluded for various reasons, and 1 publication (i.e., economic evaluation) met the inclusion criteria and was included in this report. Appendix 1 presents the PRISMA[27] flow chart of the study selection.

Summary of Study Characteristics

Additional details regarding the characteristics of the included publication are provided in Appendix 2.

Table 1: Selection Criteria

Criteria	Description
Population	Pediatric patients (< 18 years of age) with immune thrombocytopenia
Intervention	Q1: Dapsone Q2: Rituximab Q3: Thrombopoietin receptor agonists (e.g., romiplostim, eltrombopag)
Comparator	Q1: Rituximab, thrombopoietin receptor agonists Q2: Dapsone, thrombopoietin receptor agonists Q3: Dapsone, rituximab, alternative thrombopoietin receptor agonists Q1 to Q3: Placebo, IV immunoglobulin, splenectomy
Outcomes	Cost-effectiveness (e.g., cost per quality-adjusted life-year gained)
Study designs	Economic evaluations

Study Design

The economic evaluation study by Tremblay et al. (2018)[28] used a cost-consequence model to assess the cost-effectiveness in response to different treatment outcomes. The clinical data were obtained from 2 randomized placebo-controlled trials.[29,30] The indirect treatment comparison (ITC) was used to indirectly compared the clinical data of the comparators. All cost data were from US-based sources and US health care inflation of 3.6% was applied when there were no up-to-date data. No currency conversion was required. The analyses were conducted from a general US payer's perspective over a 26-week time horizon. As the model horizon was less than 1 year, discounting was not applied.

Country of Origin

The economic evaluation study[28] was conducted by authors from US.

Patient Population

Patients considered in the economic evaluation study[28] were children with chronic ITP who had insufficient response to corticosteroids, immunoglobulins, or splenectomy from 2 randomized placebo-controlled trials.[29,30] The 2 studies had some notable differences in baseline characteristics including ethnic origins, the amount of time since diagnosis, and proportion of male patients.

Interventions and Comparators

EPAG was the intervention, while ROMI and watch-and-rescue (W&R) were selected as comparators. W&R treatment was based on the placebo groups of the respective trials. Those patients would receive rescue therapy as needed.

Outcomes

The outcomes in the economic evaluation study[28] were incremental cost-effectiveness ratio (ICER), which was calculated as the incremental cost per responder, per severe bleeding event avoided, per bleeding event avoided, and per patient.

Summary of Critical Appraisal

Additional details regarding the strengths and limitations of included economic evaluation study[28] are provided in Appendix 3.

The included economic evaluation study[28] clearly stated the objective, the economic importance of the research question, the rational for choosing the alternative comparators (i.e., EPAG versus ROMI and EPAG versus W&R), and the type of economic evaluation (i.e., cost-consequence analysis) that was conducted. The model was constructed from a general US payer's perspective with a time horizon of 26 weeks. For data collection, the study clearly stated the source of effectiveness estimates with details of the design and findings (i.e., from 2 randomized placebo-controlled trials.[29,30]) The ITC technique was used to compare efficacy data between 2 trials, although there were some notable differences in baseline characteristics between trials that may affect the findings. The study clearly stated the outcome measures for economic evaluation (i.e., incremental cost per responder, incremental cost per severe bleeding event avoided, incremental cost per bleeding event avoided, and incremental cost per patient). A decision-tree model was presented with all parameters employed in the analysis. For the analysis and interpretation of results, the study clearly stated the time horizon of costs and benefits, statistical tests and confidence

intervals, justification for the choice of variables for sensitivity analysis, and the ranges over which the variables were varied. Discounting was not applicable as the time horizon was less than 1 year. The study reported incremental analysis and presented major outcomes in a disaggregated as well as aggregated form. Probabilistic sensitivity analyses (PSA) were used to address uncertainty in the analysis, with a wide range of willingness-to-pay (WTP) thresholds. The conclusion in the study was based on the data reported and was accompanied by the appropriate caveats. Overall, the study was of moderate methodological quality with respect to the study design, data collection, and analysis and interpretation of results.

Summary of Findings

Appendix 4 presents the main study findings and authors' conclusions.

Cost-Effectiveness of Dapsone for Pediatric Patients with ITP

No cost-effectiveness studies of dapsone versus rituximab or other TPO-R agonists were identified; therefore, no summary can be provided.

Cost-Effectiveness of Rituximab for Pediatric Patients with ITP

No cost-effectiveness studies of rituximab versus dapsone or other TPO-R agonists were identified; therefore, no summary can be provided.

Cost-Effectiveness of TPO-R Agonists for Pediatric Patients With ITP

For overall response (i.e., platelet counts ≥ 50 × 10^9/L without rescue medication use in the preceding 4 weeks), patients in the EPAG group had higher response rates compared to those in the ROMI group (difference of 2.3%) and W&R group (difference of 53.9%). There were fewer incidence in severe bleeding, overall bleeding, use of rescue medication in the EPAG group compared with ROMI and W&R groups. For total costs, EPAG was estimated to cost US$34,506 less than ROMI, and US$33,830 more than W&R. EPAG's lower cost compared to ROMI was largely due to lower drug costs, administration costs, costs of severe bleeding, costs of moderate bleeding, and costs of adverse events.

Cost-effectiveness analysis using ICER revealed that EPAG was dominant (i.e., less expensive, and more effective) over ROMI when assessing incremental cost per responder, per severe bleeding event avoided, per bleeding event avoided, and per patient. Uncertainty in the results was assessed via PSA, whose results were consistent with base case findings. The PSA results showed that the probabilities that EPAG being cost-effective for treating children with chronic IPT were close or equal to 100% at all WTP thresholds ranging from US$25,000 to US$10,000,000, from a general US payer's perspective. Compared with W&R, EPAG had higher total cost but had improved clinical outcomes (e.g., overall response, bleeding, and mortality). Regarding cost per severe bleeding avoided, EPAG had an ICER of US$354,197. The PSA results showed that EPAG had an ICER of 0.8% under a WTP threshold of US$100,000.

Limitations

One limitation of the economic evaluation study[28] was that there was no head-to-head trials that compared EPAG and ROMI to assess their relative efficacy and safety. The ITC technique with some inherent limitations was used to adjust the ROMI efficacy data to match the EPAG data. The technique can be biased by both observed and unobserved differences in baseline characteristics between trials. Another limitation was that this study could not include

rituximab and splenectomy, the 2 common treatments for chronic ITP, as comparators, due to unavailable data. The study used a relatively short time horizon in the model, and did not consider the indirect costs (i.e., societal perspective) in the model. Health-related quality of life was not included in the analyses. As the model was constructed from a US payer's perspective, the findings of the study may not be applicable to the Canadian context. No evidence regarding the cost-effectiveness of dapsone or rituximab was identified.

Conclusions and Implications for Decision- or Policy-Making

This report identified 1 economic evaluation study[28] using a cost-consequence model to compare the cost-effectiveness of EPAG versus ROMI in pediatric patients with chronic ITP. The study found that EPAG was dominant over ROMI (less expensive and more effective) when assessing cost per responder, cost per severe bleeding event avoided, cost per overall bleeding event avoided, and cost per patient. This was largely driven by lower drug and administrative costs and fewer severe bleeding outcomes. No cost-effectiveness studies of dapsone or rituximab for pediatric patients with ITP were identified. Future studies are needed to verify the cost-effectiveness of EPAG using different perspectives and longer time horizons, and to evaluate the cost-effectiveness of other ITP therapies including dapsone and rituximab.

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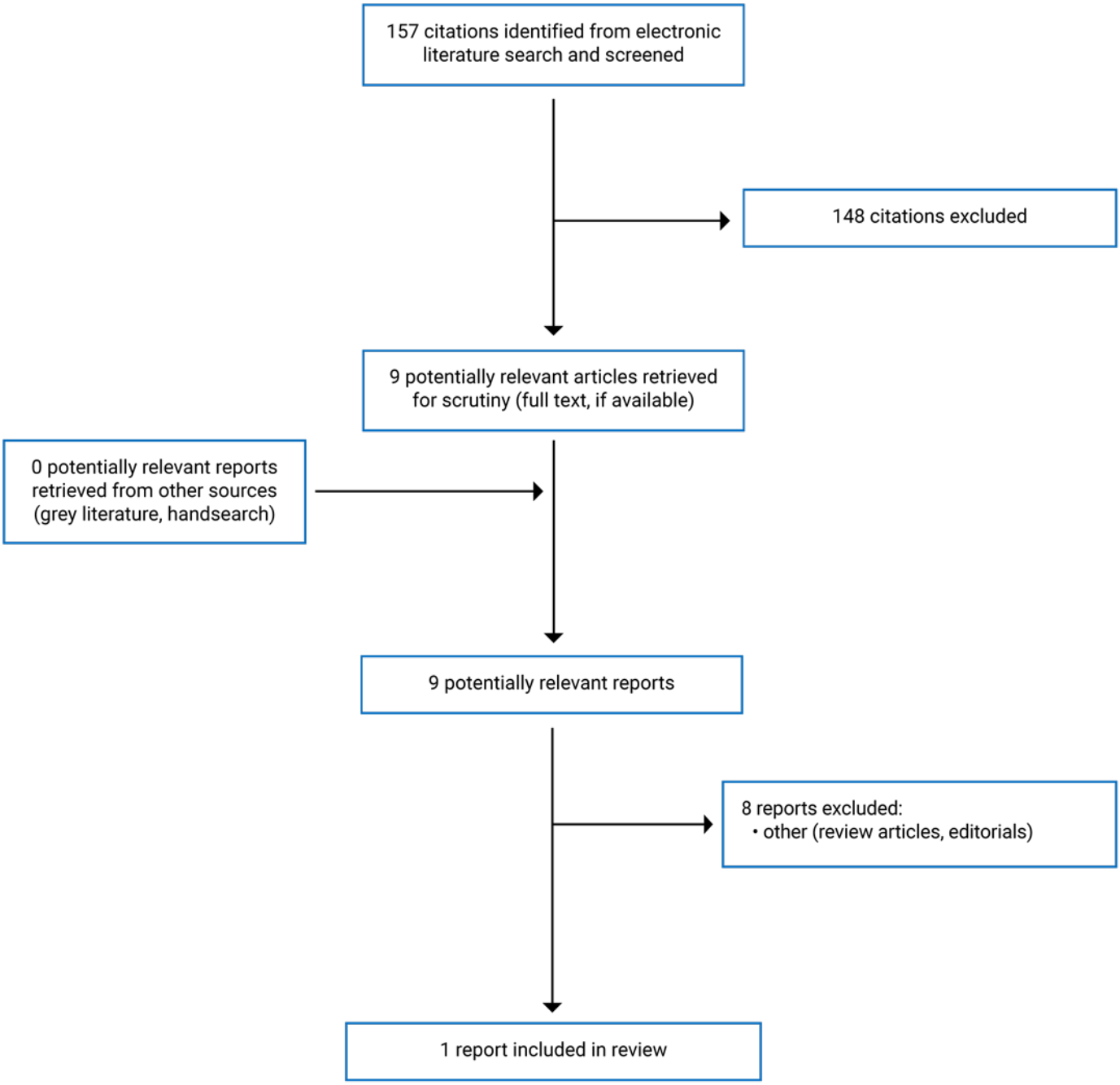
Appendix 1: Selection of Included Studies

Figure 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Economic Evaluation

Study citation country, funding source	Type of analysis, time horizon, perspective	Population characteristics	Intervention and comparator(s)	Approach	Source of clinical, cost, and utility data used in analysis	Main assumptions
Tremblay et al. (2018)[28] **US** **Novartis Pharmaceuticals**	Cost-consequence analysis Time horizon: 26 weeks Perspective: US payer's perspective Discount rate: NA	Children with chronic ITP who had insufficient response to corticosteroids, immunoglobulins, or splenectomy from 2 trials: • EPAG trial (63 EPAG-treated patients vs. 29 placebo-treated patients) ◦ Mean age: 9.6 years ◦ Males: 52% ◦ Time since diagnosis: 3.4 years ◦ East Asian: 32% • ROMI trial (42 ROMI-treated patients vs. 20 placebo-treated patients) ◦ Mean age: 8.8 years ◦ Males: 43% ◦ Time since diagnosis: 1.9 years ◦ Asian: 8%	EPAG vs. ROMI vs. W&R (placebo) EPAG (oral): 37.5 mg/day (25 mg/day for East Asians) for patients weighing less than 27 kg and 50 mg/day (25 mg/day for East Asians) for those weighing 27 kg. The dose was adjusted to 75 mg/day on the basis of individual platelet count. ROMI (SC injection): Dose adjusted weekly from 1 µg/kg to 10 µg/kg as weekly SC injection to target platelet counts of 50 to 200 x 10^9/L	The ITC technique was used to compare efficacy data between 2 trials. ICER was estimated as ratio of the difference in cost and difference in event. Cost outcomes: cost per responder, cost per bleeding event, cost per person. PSA were used to address uncertainty in the analysis, with the WTP thresholds ranging from $25,000 to $10,000,000.	Clinical data were from the EPAG trial and the ROMI trial. Severe bleeding (WHO grade 3 to 5) was the primary efficacy endpoint. Secondary efficacy endpoints were moderate bleeding and platelet response (platelet counts ≥ 50 × 10^9/L without rescue medication use in the preceding 4 weeks). All cost data were from US-based sources and US healthcare inflation (3.6%). No conversion needed. Total cost for each treatment included costs of drugs, administration, bleeding events, routine care, rescue medications, AEs (all grades), and mortality	Assumed that both clinical trials had similar baseline characteristics.

AE = adverse event; EPAG = eltrombopag; ICER = incremental cost-effectiveness ratio; ITC = indirect treatment comparison; ITP = immune thrombocytopenia; NA = not applicable; PSA = probabilistic sensitivity analysis; ROMI = romiplostim; SC = subcutaneous; vs. = versus; W&R = watch-and-rescue.

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Appendix 3: Critical Appraisal of Included Publications

Note that this appendix has not been copy-edited.

Table 3: Strengths and Limitations of Economic Evaluation Using the Drummond Checklist[26]

Strengths	Limitations
Tremblay et al. (2018)[28]	
Study design	
• The study aimed to evaluate the cost-effectiveness of EPAG in pediatric patients with chronic ITP compared with ROMI and W&R. • The economic importance of the research question was stated that there were no studies compared the cost of ROMI treatment to the cost of EPAG treatment in pediatric population. • The viewpoint of the analysis is stated that the model was constructed from a general US payer's perspective. • The comparators were clearly described (i.e., EPAG, ROMI, and W&R). • The study used a cost-consequence model to present the cost-effectiveness for various outcomes.	• As no head-to-head trials comparing EPAG and ROMI, the ITC technique was chosen to compare the data for the 2 trials comparing EPAG with placebo and ROMI with placebo, assuming both clinical trials had similar baseline characteristics. • The study was unable to incorporate rituximab and splenectomy, 2 common treatment options for chronic ITP, as comparators as there were no data available for pediatric population.
Data Collection	
• The authors clearly stated the source of clinical efficacy data, which were obtained from 2 clinical trials. • Details of the design and results of ITC were given. • The primary endpoints for the economic evaluation were ICER per responder, per bleeding event, and per patient. • All cost data are listed in USD and were derived from US-based sources (no conversions were required). US healthcare inflation at 3.6% was applied where no up-to-date data were available. • The costs incorporated and resources used are clearly described. • The study clearly described the decision-tree model with all details given.	
Analysis and interpretation of results	
• A time horizon of 26 weeks was incorporated into the model. • The study was explicit in terms of details of statistical tests and confidence intervals, approach to sensitivity analysis, choice of variables for sensitivity analysis, ranges over which the variables were varied, and incremental analysis. • Major outcomes are presented in a disaggregated as well as aggregated form. • PSA were used to address uncertainty in the analysis, with the WTP thresholds ranging from $25,000 to $10,000,000. • The results of the study answered the research question. • The conclusion was made based on reported data. • The conclusion was accompanied by the appropriate caveats.	

EPAG = eltrombopag; ICER = incremental cost-effectiveness ratio; ITC = indirect treatment comparison; ITP = immune thrombocytopenia; PSA = probabilistic sensitivity analysis; ROMI = romiplostim; W&R = watch-and-rescue.

Appendix 4: Main Study Findings and Authors' Conclusions

Note that this appendix has not been copy-edited.

Summary of Findings of Included Economic Evaluation

Tremblay et al. (2018)[28]

Main Study Findings

Cost-consequence analysis of EPAG vs. ROMI or EPAG vs. W&R

Efficacy Outcomes

- Response
  - Change (EPAG – ROMI): 2.3%
  - Change (EPAG – W&R): 53.9%
- Severe bleeding (WHO 3 to 5)
  - Change (EPAG – ROMI): -22.1%
  - Change (EPAG – W&R): -9.6%
- Moderate bleeding only (WHO 2)
  - Change (EPAG – ROMI): -15.7%
  - Change (EPAG – W&R): -8.3%
- Use of rescue medication
  - Change (EPAG – ROMI): -1.9%
  - Change (EPAG – W&R): -5.1%
- Mortality (derived from severe bleeding)
  - Change (EPAG – ROMI): -0.79%
  - Change (EPAG – W&R): -0.34%

Costs (US$)

- Drug costs
  - Change (EPAG – ROMI): -22,194
  - Change (EPAG – W&R): 40,178
- Administrative costs
  - Change (EPAG – ROMI): -1,955
  - Change (EPAG – W&R): -889
- Rescue medication costs
  - Change (EPAG – ROMI): 414
  - Change (EPAG – W&R): -1,201
- Cost of severe bleeding (WHO 3 to 5)
  - Change (EPAG – ROMI): -9,837
  - Change (EPAG – W&R): -4,259
- Cost of moderate bleeding (WHO 2)
  - Change (EPAG – ROMI): -354

- Change (EPAG – W&R): -183
- AEs costs
  - Change (EPAG – ROMI): -151
  - Change (EPAG – W&R): 373
- Mortality costs
  - Change (EPAG – ROMI): -437
  - Change (EPAG – W&R): -189
- Total costs
  - Change (EPAG – ROMI): -34,506
  - Change (EPAG – W&R): 33,830

ICER

- Incremental cost per responder
  - EPAG/ROMI: Dominant
  - EPAG/W&R: US$62,749
- Incremental cost per severe bleeding avoided (WHO 3 to 5)
  - EPAG/ROMI: Dominant
  - EPAG/W&R: US$354,197
- Incremental cost per bleeding event avoided (WHO 2 to 5)
  - EPAG/ROMI: Dominant
  - EPAG/W&R: US$189,303
- Incremental cost per patient
  - EPAG/ROMI: Dominant
  - EPAG/W&R: US$62,749

PSA Results — ICER for Costs per Severe Bleeding Avoided

- At WTP of US$25,000: EPAG was 97.5% and 0.3% cost-effective compared with ROMI and W&R, respectively.
- At WTP of US$50,000: EPAG was 98.3% and 0.5% cost-effective compared with ROMI and W&R, respectively.
- At WTP of US$100,000: EPAG was 99.2% and 0.8% cost-effective compared with ROMI and W&R, respectively.
- At WTP of US$150,000: EPAG was 99.6% and 1.5% cost-effective compared with ROMI and W&R, respectively.
- At WTP of US$250,000: EPAG was 99.9% and 14.6% cost-effective compared with ROMI and W&R, respectively.
- At WTP of US$500,000: EPAG was 100% and 79.8% cost-effective compared with ROMI and W&R, respectively.
- At WTP of US$1,000,000: EPAG was 100% and 98.8% cost-effective compared with ROMI and W&R, respectively.
- At WTP of US$10,000,000: EPAG was 100% and 99.7% cost-effective compared with ROMI and W&R, respectively.

Authors' Conclusion

"EPAG was the preferred TPO-R agonist to treat chronic ITP when indirectly compared to ROMI, largely driven by its favorable severe bleeding outcomes and lower drug and administration costs."[28] (p. 715)